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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,592
Filing Date: May 03, 2002
Appellant(s): GODDARD ET AL.

Anne Marie Kaiser
For Appellants

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 05, 2005, appealing from the Office action mailed November 08, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner as provided by the Appellants which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

A Notice of Appeal has been filed in the related Application Nos. 10/063,570, 10/063,607, 10/063,640, 10/063,647, 10/063,666, 10/063,668, 10/063,519, 10/063,560, and 10/063,713. A Notice of Appeal and an Appeal Brief have also been filed in the related Application Nos. 10/063,530, 10/063,540, 10/063,578, 10/063,584, 10/063,616, 10/063,648, 10/063,652, 10/063,653, 10/063,659, 10/063,534, 10/063,586, 10/063,587, 10/063,591, 10/063,660, 10/063,587, 10/063,592, 10/063,616, 10/063,617, 10/063,524, 10/063,534, 10/063,584, 10/063,586, and 10/063,661.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Haynes et al., Proteome analysis: Biological assay or data archive, Electrophoresis, 19:1862-1871, 1998.

Hu et al., Analysis of genomic and proteomic data using advanced literature mining, J. Proteome Res., 2:405-412, June 2003.

Fessler et al., A genomic and proteomic analysis of the activation of the human neutrophil by lipopolysaccharide and its mediation by p38 mitogen-activated protein kinase, J. Biol. Chem. 277(35):31291-31302, 30 Aug. 2002.

Alberts et al. Molecular Biology of the Cell, 4rd Edition 2002 (New York:Garland Publishing), pp. 302, 363-364, 379, 435.

Alberts et al. Molecular Biology of the Cell, 3rd Edition 1994 (New York:Garland Publishing), pp. 403-404, 453.

B. Lewin, Genes VI, 1997.

Zhigang et al., World Journal of Surgical Oncology, 2: 13, 2004.

Meric et al., Translation initiation in cancer: A novel target for therapy, Molecular Cancer Therapeutics, 1:971-979, 2002.

Gygi et al., Correlation between protein and mRNA abundance in yeast, Mol. Cell. Biol., 19(3):1720-1730 Mar. 1999.

W0 00/70049 Incyte Genomics, Inc. 11-2000.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

Claims 1-5 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to an antibody which specifically binds the polypeptide of SEQ ID NO:82. The specification asserts a number of utilities for both the polypeptide and encoding polynucleotide, however, these utilities are not specific and substantial or well established. If the polypeptide antigen does not have utility, then the antibody which binds it does not have a specific and substantial utility. For example, in Example 10 (pages 132-133), it is asserted that the polypeptide may be used as an antigen to make antibodies. Because neither the physiological nor the clinical significance of the polypeptide is known, and because the prior art does not support a very close structural relationship to a well described family of known proteins by both structure and function, the polypeptide does not have utility as required by 35 USC 101. If one does not know what the protein to which the antibody binds does or what disease it is specifically associated with, then the antibody that binds the protein likewise does not have utility. The ability to isolate a protein, detect expression changes of the protein and diagnose disease by using an antibody is not a specific or substantial use if it is not known what the isolated or expressed protein does or what specific disease can by diagnosed with it.

Another asserted utility is in drug screening and rational drug design (Examples 12 and 13, respectively). The methods involve screening for "agents which can affect a PRO polypeptide-associated disease or disorder" (p. 135, ¶[0507]). No disease or disorder is known to be associated with the claimed polypeptide or encoding polynucleotide. In order to discern a utility for the claimed polypeptide through drug screening in the absence of guidance about which type of disease or disorder the polypeptide causes or how its involvement could lead to treatment, screening for drugs by using the polypeptide would still require further and undue

experimentation to determine the significance of an agent that somehow influenced the polypeptide's function.

Another possible utility comes for the finding that the encoding polynucleotide, DNA 64902-1667, is "more highly expressed" in esophageal or kidney tumor tissue as compared to normal esophagus and kidney tissue (Example 18, p. 142). There is no guidance on how to use this information. No levels (relative or absolute) are disclosed. This information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for esophageal or kidney tumor. Further, even though the polynucleotide has utility, it has no enabled use as a tumor marker and the encoded polypeptide has no such utility since one skilled in the art would not reasonably expect that there is alteration of polypeptide sequence or amount in esophageal or kidney tumor *versus* normal tissue. The polypeptide shares no high amount of structural relatedness to a prior art protein which has a known functions, so that the prior art cannot provide insight into the activity of the claimed protein. It is not known what the protein does or if the level of the protein of SEQ ID NO:82 in esophageal or kidney tumors corresponds to nucleic acid transcript level, *i.e.*, if increased mRNA in tumors corresponds to an increased amount of expressed protein. Also, while a signal peptide was identified as amino acids 1-25 of SEQ ID N0:82 (Fig. 82), the specification does not provide information about whether the protein is transported to or through the cell's membrane.

The instant specification provides no specific information regarding increased mRNA or protein levels of PRO1557 in tumor samples relative to normal samples. Only vague relative gene expression data was presented. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412, cited by Examiner in the paper mailed 1/13/05) analyzed 2286 genes which showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). However,

in the instant application it is not disclosed whether or not the polypeptide levels correlate with nucleic acid (either DNA or mRNA) levels. So one cannot base the use of the polypeptide on the expression of the nucleic acid.

There is influential prior art to support the unpredictibility concerning the correspondence of mRNA to protein levels. For example, Haynes et al. (Electrophoresis 19 : 1862-1871 , 1998, cited by the Examiner in the paper mailed 07/06/05) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Haynes et al. provides evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Additionally, Fessler et al. (J. Biol. Chem. 277(35): 31291-31302, Aug. 2002, cited by the Examiner in the paper mailed 07/06/05) who examined lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on p. 31300) stated, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." Fessler et al. warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels."

Given the unknown amount that mRNA of PRO1557 increased in tumors, and the unpredictability about correlating mRNA to protein levels as exemplified by Haynes et al., Hu et al., and Fessler et al., one skilled in the art would not have assumed that a small increase in mRNA would correlate with significantly increased polypeptide levels. Such further research requirements make it clear that the asserted utility is not yet in currently available form, *i.e.*, it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellants' claimed invention is incomplete. The instant situation is directly

analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Note that the invention must have a specific and substantial utility.

For these reasons, there is no substantial and specific utility for the claimed polypeptide.

Claim Rejections - 35 USC § 112

Claims 1-5 remain also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed antibody because no definite function or directly associated disease has been determined for the protein of SEQ ID NO:82 to which the antibody binds, and there is no definite function supported by the prior art. No function can be reasonably assigned based on its homology to another protein(s).

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is an antibody which binds a polypeptide encoded by a nucleic acid with no known specific association other than that asserted by Appellants of higher expression in kidney and esophageal tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in kidney and esophageal tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical

property. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though no tumor markers were identical or highly similar to SEQ ID NO:81. Therefore, the connection of SEQ ID NO:81 to tumors was not known. The prior art is silent with respect to activity of PRO1557 or its relationship to a family of proteins with conserved structure and function. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. There is very little guidance or direction about using the claimed polypeptide except that nucleic acid of SEQ ID NO:81 which encodes the polypeptide is more highly expressed in kidney and esophageal tumors. The specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

Claim Rejections - 35 USC § 102

Claims 1-5 remain are rejected under 35 U.S.C. 102(b) as being anticipated by WO 200070049.

WO 200070049 teaches the protein of SEQ ID NO:13 (encoded by the nucleic acid sequence of SEQ ID NO:39) which is 100% identical SEQ ID NO:82 of the instant application, with the signal sequence designated as amino acids 1-25 (Table 2 of WO), as well as an antibody that specifically binds to the protein (*e.g.*,p. 62, line 24-p.63, line 4). These antibodies taught include monoclonal, humanized, labeled and antibody fragments (p. 39, lines 30-through p. 40, line 19, p. 19, lines 27-29, p. 46, lines 13-15).

(10) Response to Argument

Appellants argue (page 6) that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." The specification has failings which the Examiner pointed out. While current availability of a claimed invention is not always necessary, the invention must still meet the requirements of 35 USC 101 and 112, first paragraph. For the reasons discussed here and in the previous Office action, it is maintained the specification does not support utility or contain an enabling disclosure, and the evidence submitted, including declarations, does not overcome the insufficiencies of the disclosure. While other asserted utilities were discussed in previous Office actions such as drug screening and microarray analysis, these utilities are not substantial for the reasons previously stated.

Appellants argue (bottom of p. 6 through p. 7, and paragraph bridging pages 9-10) that statements of utility are presumed to be true unless they are incredible. The argument has been fully considered, but is not persuasive. Credibility has not been raised as an issue.

Appellants argue (bottom of p. 10) that because the PRO1557 mRNA was held to have utility, the claimed antibody, which binds the encoded polypeptide, has a specific utility as a cancer diagnostic too, particularly for kidney and esophagus. The argument has been fully considered, but is not persuasive. While it is agreed that the polynucleotide of SEQ ID NO:81 has utility because of some level of its differential expression in tumor compared to normal tissue, it is not agreed that the polypeptide of SEQ ID NO:82 does. The reasons for this have been discussed above, including unknown relative or absolute levels of the difference(s) in PRO1557 protein level in tumor compared normal kidney and esophagus tissue, the lack of information about particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), the lack of information about repeatability of the differential expression both in terms of

frequency/prevalence and quantity/sensitivity, unknown necessary sample size or expression level range for normal and tumor tissues and the unpredictability of correlation mRNA and protein expression levels, it is maintained that the claimed invention is not supported by a substantial or specific utility nor is it enabled.

Appellants argue (p. 9 and bottom of p. 56) that the specification discloses that PRO polypeptides may by used to generate anti-PRO antibodies which are useful as diagnostic tools. The argument has been fully considered, but is not persuasive. If the claimed protein to which an antibody binds is not enabled for how to use and lacks utility, then the antibody likewise has no use. The sole ability to bind a protein is not sufficient to support enablement or a substantial utility.

Appellants argue (pages 10-11) that the data of Example 18 showing higher expression of PRO1557 nucleic acid in tumor *versus* normal tissue is not based on gene amplification but on cDNA or mRNA levels compared to protein levels. Appellants further state that the Examiner interpreted the data and cited references, focusing on gene copy number instead of mRNA levels, citing the first paragraph of the Final Office action mailed 7/6/05 as evidence of this. The argument has been fully considered, but is not persuasive. The Examiner in the Final Office action made a obvious error by referring to copy number instead of gene expression (*i.e.*, mRNA). For example, in the First Office action on the merits mailed 1/13/05, the Examiner states on page three, second paragraph, "It is important to note that the instant specification provides no information regarding increased mRNA or protein levels of PRO1557 in tumor samples relative to normal samples. Only relative gene expression data was presented." Also, in the Final Office action toward the bottom of page 7 in addressing the Declaration of Grimaldi, the Examiner acknowledged that, "Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues, this does not fill the above discussed gaps." Further, the references discussed in previous Office actions by the Examiner analyze the correlation between mRNA and protein, not gene copy number. As previously discussed, Haynes et al. supports the inability to reasonably expect the level of mRNA to correspond to the level of its encoded protein. Fessler et al. examining lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on p. 31300) states, "Parallel use of

DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." Fessler et al. warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." Given the unknown amount that mRNA copy number of PRO1557 increased in tumors, and the evidence provided by Haynes et al., Hu et al. and Fessler et al., one skilled in the art would not have assumed that a small increase in mRNA copy number would correlate with significantly increased polypeptide levels. The level of increase of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO1557 polypeptide levels increased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, *i.e.,* it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellants' claimed invention is incomplete. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form that can be used without necessary further experimentation.

Appellants argue on pages 12-13, 29-30 and 37 that *In re Brana* states that the USPTO has the initial burden of showing "that one of ordinary skill in the art would reasonably doubt the asserted utility." The argument has been fully considered, but is not persuasive. *Brana* dealt with a rejection under 35 USC 112, first paragraph, the rejection was directed toward utility--specific, substantial and credible use. While it is true that administration of a pharmaceutical to a human is not always necessary for either utility or enablement nor that a protein have been used diagnostically, one must know how to use the invention without undue experimentation. In the instant situation, Appellants claim a polypeptide about which the USPTO has presented evidence (*e.g.*, Haynes et al., Hu et al. and Fessler et al.) showing that for eukaryotic polypeptides in general one cannot assume that it is more likely than not that the polypeptide will have a level of expression comparable to that of its encoding mRNA in one tissue type compared to a matched tumor tissue type even if the encoding nucleic acid in the normal and tumor tissues does have

detectably different expression levels. The USPTO has met the burden of showing one skilled in the art would reasonably doubt the asserted utility by showing that the correspondence between mRNA and protein levels is not predictable as previously discussed.

Appellants argue (pages 14 -15) that the PTO maintains that the specification fails to provide particular "critical information" and the PTO has applied an improperly high standard by requiring additional data and evidence be disclosed in order for Appellants to initially establish a utility for the claimed polypeptides, while all the courts require is an asserted utility presumptively correct. The argument has been fully considered, but is not persuasive. Utility requires more than assertion, it requires that the assertion and support in the specification be sufficient to establish a specific and substantial or a well-established use for the claimed invention. It is maintained the requirements for utility have not been satisfied in the instant case for the reasons of record. There are a number of significant unknowns in the specification which the declarations, exhibits and arguments do not fill. One example is that there are several types of cancers for any type of tissue, for example, squamus cell or adenocarcinoma, and the type which was identified in the instant application is not disclosed. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated previously, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels in normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a currently available form. Other gaps in information include, for example, tumor type (etiology), repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and a basis for reasonably expecting that a change in mRNA level causes a corresponding change in protein

level. It is maintained that significant further research would be necessary to use the claimed invention.

Appellants argue (p. 14 and end of p. 18 through p. 19) that the Examiner does not rely on evidence in rejecting the claimed antibodies as lacking utility. The argument has been fully considered, but is not persuasive. Whether Fessler et al. or Haynes et al., for example, were used in rebuttal to Appellants' previous arguments or in the rejection, they serve as evidence that correlation of levels between mRNA and encoded protein is unpredictable.

Appellants argue (bottom of page 14 through 15) that neither Hu et al. (cited in the original rejection) nor Fessler et al. or Haynes et al. discussed in subsequent Office actions serve as a basis for the utility rejection. The argument has been fully considered, but is not persuasive. Appellants citation of the Examiner from the Advisory Action (p. 2) saying Fessler and Haynes were not part of the rejction is taken out of context. The Examiner was addressing Appellants' accusation that a new grounds of rejection had been made since new references were discussed after the first Office action on the merits. As stated in the first paragraph of p. 6 of Appellants' response filed 10/17/05, "Because the PTO has presented new arguments and evidence, and is making assertions of fact not relied on in the previous Office Action, Applicants submit that the finality of the present rejection is improper." The Examiner was explaining why the discussion of the references did not prevent the holding of finality. The references of Hu et al., Fessler et al. and Haynes et al. are pertinent to the rejection of claims under 35 USC 101 and 112, first paragraph, as previously discussed; that is, they support of the unpredictability of the correlation of levels of mRNA and corresponding protein. A utility rejection is not based on prior art. Only rejections under 35 USC 102 or 103 are based on prior art.

Appellants argue on pages 15 and 30 that the PTO has not met the initial burden of refuting that it is more likely than not the claimed polypeptide does not have the asserted utility and that there is no evidence of record to establish that one of ordinary skill in the art would reasonably doubt that the disclosed polypeptide is differentially expressed in certain tumors and can be used as a diagnostic tool. The argument has been fully considered, but is not persuasive. One should not confuse credibility with specific and substantial use or enablement. The Examiner maintains that as a whole, the prior art does not provide a reasonable expectation that the level of expression of the nucleic acid of SEQ ID NO:81 positively correlates with the level

of expression of the protein of SEQ ID NO:82. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. Protein levels do not need to be "accurately" predicated, but relative or absolute levels or information about repeatability are critical for the skilled artisan to be able to use the instant invention without having to do further significant research. While absolute values are not necessary, certain criteria must be met for relative levels to be meaning for in terms of utility. Some criteria include what the relative difference is (*e.g.*, 0.5 times more or 10 times more expression), repeatability (*e.g.*, how may different esophagus or kidney tumor samples were used), whether the claimed polypeptide is more highly expressed in the tissues in which that the PRO1557 polynucleotide is more highly expressed.

Appellants argue (top of page 16 and middle of p. 30) that the results of Hu et al. (J. Proteome Res., 2003) are not surprising and provide little if any information about genes with 2-fold or more differential expression in tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are statistically significant.

Appellants argue (pages 16-17) that the results of Hu et al. do not show a lack of correlation between microarray data and biological significance, have statistical flaws and are applicable only to estrongen-postive breast tumors. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are statistically significant. While Hu et al. examined just one kind of cancer, the results taken together with others discussed by the Examiner, support the inability of the skilled artisan to make assumptions about the correlation of nucleic acid expression data with expressed protein

data. While neither a gene nor the encoded protein need to have a biologically meaningful role in disease, one skilled in the art must be able to use it and it must be supported by a substantial utility.

Appellants argue (pages 17-18) that the role of a gene in a cancer is not necessary to enable its use as a diagnostic tool for tumor detection. The argument has been fully considered, but is not persuasive. It is correct that the role of a gene need not be known, but the specification and/or prior art needs to enable that particular gene to be used diagnostically. In this case, the prior art provides no information about the use of the gene and the specification does not provide an enabling disclosure for use of the PRO1557 nucleic acid or protein as a diagnostic tool for kidney and esophagus tumors based on differential expression for the reasons discussed above and in previous Office actions. As to the claims drawn to proteins not identical to SEQ ID NO:82, even if SEQ ID NO:82 was enabled for a diagnostic tool, proteins not identical would not be enabled because they would not be expected to be present in tumors and what parts of the protein are antigenic and necessary for proper antibody binding (and production) for the protein to be useful as an antigen to make antibodies that would recognize the protein of SEQ ID NO:82 are not disclosed.

Appellants argue (top of p. 18) that the utility of a nucleic acid does not depend on the function of the encoded gene product. A utility example from Utility Guidelines is described in which a DNA may have utility if it hybridizes near a disease-associated gene or has a gene regulating activity. While this argument is true, it does not provide a basis for utility for the claimed antibody. While utility of a nucleic acid does not necessarily depend on the function of the encoded protein, the encoded protein cannot depend on utility of the nucleic acid if the protein cannot share the same utility. In the instant case, it is maintained for the reasons of record that even though the nucleic acid may have utility because it is more highly expressed in certain cancer tissues, the encoded polypeptide does not because it is unpredictable whether it also shares the characteristic of higher expression in the cancer tissues.

Appellants argue (middle of p. 18) that like "the mere identification of a pharmacological activity", identification of an altered expression provides 'immediate benefit to the pubic'. See MPEP § 2107.01. The argument has been fully considered, but is not persuasive. This citation relates to the Court's decision in *Nelson v. Bowler.* In that decision, the CCPA says that specific

therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. In this instance, pharmacological activity is not the same as altered gene expression. In *Nelson,* the court held that the compound of which utility was in question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility. There are no test results to correlate the presence of PRO1557 polypeptide with a diagnostic for kidney or esophagus tumor. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:82 and utility as a cancer diagnostic. The findings of higher expression of the nucleic acid of SEQ ID NO:81 cannot be assumed to correlate to the higher expression of the encoded polypeptide in the same tissues.

Appellants argue (pages 20-21) that because the coding region of BNF-1 taught by Wu et al. (Gene, 2003, part of paper mailed 1/13/05) is identical to the coding region of SEQ ID NO:81 and Wu et al. demonstrates overexpression of BNF-1 nucleic acid in some tumor samples, the BNF-1 nucleic acid supports utility of the nucleic acid of SEQ ID NO:81 as a tumor marker and supports the utility of the polypeptide. Appellants state (bottom of p. 22) that "the teachings of Wu are fully consistent with Appellants' disclosure." It is further argued (first paragraph of p. 23) that Wu did not pool samples and used a higher threshold of differential expression, concluding that "the threshold used in Appellants' experiments requires higher and/or more consistent differential expression than Wu." The argument has been fully considered, but is not persuasive. Appellants explain that the specification showed an at least 2-fold difference. This, however, is lower or the same as the 2- to 4-fold difference shown by Wu (p. 107, col. 2, last paragraph, and p.109, col. 1, first two paragraphs). While Wu et al. found differences in breast, lung and colon tumor *versus* normal tissue, the Inventors did not, even though it appears that at least lung was tested as shown by other DNAs having lung expression in Example 18 of the instant application. It is not clear if the discrepancy is caused by different methodology, pooling of samples by Appellants or use of different tumor sources, for example. As previously discussed, the specification is silent with respect to necessary sample size, expression level range

for normal and tumor tissues, types of kidney or esophageal tissue that can used, and other questions. Nor does it support a specific and substantial utility.

Appellants argue (middle of p. 21) that "The Examiner criticizes Appellants' disclosure as not sufficiently sensitive to detect the differential expression reported in Wu," but too sensitive based on the interpretation of Hu et al. The argument has been fully considered, but is not persuasive. This is not correct. The Examiner maintains that one cannot determine if the results of Example 18 are statistically significant and therefore cannot support enablement as a tumor marker or in a role in tumor formation or progression. Assay sensitivity and repeatability are valuable in interpretation of data. Wu et al. did not pool samples but showed the sensitivity that would be expected in a clinical setting. That is, if one is attempting to use a probe as a cancer diagnostic, one would not pool the tumor tissue from multiple patients in order to diagnose each individual. One must use individual samples, as Wu did, to determine if an individual patient has cancer. As previously discussed in reference to the Declaration of Grimaldi in the Final Office action in the last paragraph of page 8, "The declaration also says (¶5) that "Data from a pooled sample are more likely to be accurate than data from a single individual." This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not usually geared toward a populous but toward an individual's particular condition." On page 11, first paragraph, it is pointed out that because the samples in the instant application were pooled for analysis, "As discussed above, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO1557 nucleic acid and/or protein."

Appellants argue (pages 22-24) that the report of Haynes et al. and Gygi et al. (filed by Appellants in the IDS of 4/13/05) do not support the Examiner's position that mRNA levels do not correlate with protein levels, pointing out that Haynes did not look at *single* genes and corresponding protein level. Appellants point to the correlation coefficient of 0.935 in Haynes et al., saying that this shows a correlation instead of the lack of one. The argument has been fully considered, but is not persuasive. A complete reading of Haynes and Gygi et al. continues to support the reliance on Haynes et al. A full reading of Gygi et al. clarifies the data (p. 1726, first full paragraph):

> For the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data set (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was 0.356.

Contrary to Appellants' assertion that Figures 5 and 6 of Gygi support the correlation of mRNA and protein levels, Gygi et al. show in Figure 5 the same figure as Fig. 1 of Haynes and show in Fig. 6, what is described for the Pearson correlation coefficients in the cited paragraph above. Gygi et al. say beginning in the last sentence in col. 1 of p. 1727 that, "The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." As to correlation of an individual gene, Gygi et al. and Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described above by Haynes et al. Each point in the figures of Haynes et al.and Gygi et al. are individual genes (see Fig. 1 and Figs. 5-6, respectively). Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1557 nucleic acid was isolated).

Appellants also argue (pages 23-24 and bottom of p.28) that Haynes et al. is not relevant to the instant application since yeast cells were used and did not compare mRNA and protein levels from the same yeast cells. Additionally, Haynes et al. discuss only steady-state levels, which is a different issue than the changing levels discussed by Appellants. The argument has been fully considered, but is not persuasive. Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the

low 0.356 correlation coefficient described by Haynes et al. Each point in the figures of Haynes et al. is an individual gene (see Fig. 1). Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results, which are from eukaryotic cells, are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1557 nucleic acid was isolated). The instant specification did not show that changing levels of PRO1557 mRNA lead to respective changing levels in PRO1557 protein. It showed that there is some unknown amount of SEQ ID NO:81 produced at a lower level in normal kidney and esophagus than in kidney and esophagus tumor tissue. The unknowns continue in terms of samples used, repeatability, sensitivity, unknown relative or absolute amounts of mRNA in the tissues, etiology of tumor tissue used, and whether the difference extends to the a difference in encoded protein levels.

Appellants argue that evidence of changes in protein levels when mRNA levels are unchanged has no relevance to Appellants' assertion (paragraph bridging pages 24-25). The argument has been fully considered, but is not persuasive. As discussed by Gygi et al. (last sentence in col. 1 of p. 1727), "The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." As explained by Gygi et al., there are a number of post-translation mechanism that can causes differences in mRNA compared to protein levels. Such mechanisms influence the unpredictability of whether mRNA and encoding protein levels correlate.

Appellants argue (pages 24-27 and end of p. 28) that Fessler et al. shows that in 5/6 cases for which change in mRNA levels was reported, the change corresponded to change in protein level. Appellants state that, "Nothing in these results by Fessler suggest that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein." For 6 samples in Table VIII of Fessler, mRNA was "absent" so that correlation with protein is not applicable. The argument has been fully considered, but is not persuasive. As noted by Appellants (last paragraph of p. 26), "Of 13 up-regulated proteins, a change in mRNA levels is reported in only 3 such proteins. For these 3, mRNA levels were

increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels are also decreased." Also, of the 13 up-regulated proteins, 5 corresponding mRNAs were unchanged and 5 were not detected ("absent"). That means, disregarding the undetectable mRNAs, for 8 up-regulated proteins, only 2/13 showed corresponding upregulation in mRNA levels. The odds were slightly better for the 5 down-regulated proteins, with 3 corresponding mRNAs also down-regulated, 1 unchanged and 1 undetectable ("absent"). So 3/5 down-regulated proteins showed corresponding down-regulation in mRNA levels. (See paragraph bridging cols. 1-2 of p. 31295 of Fessler for data.) One can hardly conclude that the results of Fessler support that the change in levels of particular encoding mRNAs generally leads to a corresponding change in levels of the proteins. Indeed, what the results of Fessler et al. show is that a change in mRNA level does not necessarily have a corresponding change in protein levels and *vice versa*. This supports the high unpredictability for correspondence of protein and mRNA levels. When the findings of Fessler et al. are viewed with the findings of others such as Hayes et al. (previously cited) in the relatively new field of proteomics, the "...art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:81 positively correlates with the expression of the protein of SEQ ID NO:82. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma." (top of p. 6 of Advisory action mailed 11/8/05)

Appellants argue (page 26) that there are "limitations" in the technique used by Fessler et al., including possible artifactual transcript-protein discordance due to a 4 hour delay in harvesting after LPS exposure, uncertain post-incubation but pre-electorphoresis effects on protein synthesis, degranulation and exocytosis; and limited ability to quantitate protein amounts using Coomassie Blue (Fessler at 31301, left col.). The argument has been fully considered, but is not persuasive. As to Coomassie Blue staining, Fessler says it should be considered "semi-quantitative" (middle of col. 1, p. 21301). Appellants' results of Example 18 are also semi-quantitative as stated by Grimaldi in paragraph 6 of the Declaration filed 4/13/05 as an exhibit. Fessler et al. attempted to limit problems associated with lowered sensitivity by using only those spots which were common to all twelve pH3.0-10.0 two-D gels and which met statistical significance criteria (p. 31301 end of first full paragraph). The findings in general show that

post-transcriptional and –translational modifications play an important role in biological influence of the encoding nucleic acid and encoded protein (*e.g.*, p. 31301, middle of last paragraph). It is concluded that (p. 31301, col. 2), "Although gene expression appears to be an important mecha- nism by which PMNs respond acutely to infection, mRNA transcript/protein concordance is limited, and post-transcriptional (and post-translational) modifications also play an important role." The reference reinforces the complexity of translational factors and supports the warning concerning the inability to drawing conclusions about protein levels based on mRNA levels.

Appellants argue (pages 29033, 36 and 48) that it is "more likely than not" that the expression of the polypeptide will correlate with encoding nucleic acid expression in tumors (*i.e.*, at increased levels) and that the law does not require absolute levels of expression. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential art of record that requires the Examiner maintain that as a whole, the art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:81 positively correlates with the expression of the protein of SEQ ID NO:82. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. Neither protein nor nucleic acid levels need to be "accurately" predicated, but relative or absolute levels or information about repeatability are critical for the skilled artisan to be able to use the instant invention without having to do further significant research. While absolute values are not necessary, certain criteria must be met for relative levels to be meaningful for in terms of utility. Some criteria are what the relative difference is and repeatability (*e.g.*, how may different tumor samples were used).

Appellants argue (pages 31-32 and 37) that paragraphs 6 and 7 of the first declaration by Dr. Grimaldi (submitted 4/13/05) explains that the semi-quantitative analysis used for Example 18 of the instant application is sufficient to determine if a gene is over- or under-expressed in a tumor compared to normal cell, with detectability of at least 2-fold differences, and the relative not the absolute difference is what matters. This argument has been fully considered but is not deemed persuasive. The conclusory statements in the declaration do not support a substantial

utility or enable the invention because they do not fill important gaps in the disclosure needed to allow the skilled artisan to use the invention without significant further experimentation, such as expression level range for normal and tumor tissues, specific types of kidney and esophagus tumors detectable, and probability of detection for any particular kidney or esophageal tumor type (*e.g.*, whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested). Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues. This information does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as "semi-quantitative" and the specification for Example 18 as "standard quantitative". The declaration also says (¶5) that "Data from a pooled sample are more likely to be accurate than data from a single individual." This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of esophageal and kidney tissue that can used, and other questions, the specification has not provided the invention in an enabling or substantial form. Even if tissue samples are pooled, about which the first Grimaldi Declaration says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance. If a clinician took a kidney tissue sample from an individual patient with suspected kidney cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO:81 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? While the sixth paragraph of the first Grimaldi Declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a

specific and substantial use of the nucleic acid in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of kidney and esophagus tissue that can used, and other questions, the specification has not provided the invention in a form readily usable by the skilled such that *significant* further experimentation was unnecessary. Therefore, even accepting Dr. Grimaldi's opinion, the declaration is insufficient to overcome the rejection of the claims under 35 USC 101 and 112, first paragraph, for the reasons discussed above. It is noted that Dr. Grimaldi is an inventor of the instant application.

Appellants argue (top of p. 39) diagnosis of an individual's disease is based on disease indicators derived from characteristics of a populous. This argument has been fully considered but is not deemed persuasive because indicators are generally not from pooled samples but analysis of many individual samples. Thus the skilled clinical or researcher can analyze statistical significance as well as look for outliers, *etc.* As discussed in previous Office actions and above, one cannot tell from the pooled data of Example 18 probability of whether one would reasonably expect higher expression to be found in 10/10 or 1/20 tumors tested, for example.

Appellants argue (pages 32 and 39-40) that "Office personnel must accept option from a qualified expert that is based upon relevant facts whose accuracy is not being questions." First, it is important to note that the instant specification provides no specific information regarding increased mRNA levels of PRO1557 in tumor samples relative to normal samples. Only gene expression data represented as "more highly expressed" was presented. Second, the declaration does not provide data such that the Examiner can independently draw conclusions. Only Dr. Grimaldi's conclusions are provided in the declaration. While several articles are provided as evidentiary support to Dr. Grimladi's statement that it remains a dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide (¶5), two of the references are discussed below and do not address the lack of substantial utility or enablement of PRO1557 polypeptide. While one can find references that support Dr. Grimaldi's statements, other previously cited literature illustrates the unpredictability inherent in correspondence between mRNA and protein levels.

In the second Declaration of Dr. Grimaldi submitted 4/13/05, Appellants argue (pages 33, 40 and 48) that increased or decreased gene expression correlates with increased or decreased polypeptide expression, respectively, in a vast majority of the cases. Also, paragraph 4 of the declaration describes mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, not a readily available utility. The PRO1557 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t(5;14), no chromosomal translocation of PRO1557 is known to occur. Paragraph 6 of the declaration says that even when amplification of a cancer marker gene does not result in significant over- or under-expression of the corresponding gene product, that in itself provides important information for cancer diagnosis and treatment. However, there is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene

product. This is a hypothetical utility not disclosed in the specification. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. It remains that, as evidence by Haynes et al. and Fessler et al., for example, the issue is simply not predictable, and the specification presents a mere invitation to experiment. This is further borne out in paragraph 6, which proposes further experimentation, should Appellants' assertions be erroneous. As can be seen from previous Office actions (*e.g.*, 07/06/05), the concepts set forth in the second Dr. Grimaldi declaration and all other declarations had been addressed and not found persuasive as additionally discussed in this Answer.

Appellants argue (pages 33 and 39) that the declaration by Dr. Polakis also submitted as an exhibit 4/13/05 supports both utility and enablement of the instant invention. In the declaration Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. The declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Appellants cite Alberts et al. (Molecular Biology of the Cell, 1994 and 2002, filed in the IDS of 4/13/05) for showing the steps at which eukaryotic gene expression can be controlled,

correlating transcription with protein production (p. 34 of Brief). This argument has been fully considered but is not deemed persuasive. It is noted that the field of proteomics was very new in 1994, when the first cited teachings of Alberts were published. Additionally, the references of Haynes et al. and Fessler et al. clearly show that one cannot reasonably expect that for any given mRNA the level of protein produced therefrom will correlate with the amount of mRNA.

Appellants also cite Lewin (Genes VI, 1997, filed in the IDS of 4/13/05) and Zhigang et al. (World J. Surg. Oncol, 2004, filed in the IDS of 4/13/05) to support the ideas of Alberts et al. (above), with the example of Zhigang et al. showing that there is a high correlation between PSCA protein and mRNA expression (pages 35 and 40 of Brief and end of p. 37, dealing with lack of explanation of why gaps in the specification need to be filled). This argument has been fully considered but is not deemed persuasive. Lewin teaches the same idea that Alberts et al. do. As Appellants quote Lewin in the middle of page 36 of the Brief, "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." Genes V1 at 847-848 (emphasis added by Examiner). Lewin says that one cannot presume a correlation between RNA and protein, even though most regulator events occur when DNA is transcribed. There is convincing evidence of record that in some cases transcription is the controlling factor but in other it is translation. Zhighan find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application we have no correlation. There is no suggestion in the specification of multiple tumors tested. There are [0530] just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO1557 nucleic acid and/or protein. If Zhinghan et al. had obtained only a 5% correlation, it is doubtful he would have concluded that the nucleic acid would be a promising molecular marker.

Appellants argue (pages 35 and 41) that Meric et al. (Mol. Cancer Ther., 2002, filed in the IDS of 4/13/05) says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this statement is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use as discussed above and the art that teaches unpredictability concerning a correlation between protein and mRNA expression levels. Further reading of Meric et al. seems to teach away from Appellants' claim that there is a correlation between increased mRNA level and protein level. For example, Meric et al. discloses that variation in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974).

Appellants argue (p. 36) that the asserted utility is specific. It is specific to kidney and esophageal tumor(s), though it is maintained that is not substantial or enabled for the reasons discussed in previous Office actions and here.

Appellants argue (pages 41-42) that the Examiner has dismissed textbook references, articles and declaration in maintaining the rejections. The argument has been fully considered, but is not persuasive. There are a number of significant unknowns in the specification that the declarations, exhibits and arguments do not solve. One example is that there are several types of cancers for any type of tissue, for example, squamus cell or adenocarcinoma, and the type which was identified in the instant application is not disclosed. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966) 696, in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated previously, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues,

the specification has not provided the invention in a currently available form. Other gaps in information include, for example, tumor type (etiology), repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and a basis for reasonably expecting that a change in mRNA level causes a corresponding change in protein level.

Appellants argue (page 42 and paragraph bridging pages 47-48) that in *Brenner v. Manson*, 383 US 519, 148 USPQ 689 (1966) at 691, the Court held that "where a claimed process produces a known product it is not necessary to show utility for the product." Appellants say the Examiner points to no facts whatsoever in the decision to support the position that finding in *Brenner* are analogous to the instant application. The argument has been fully considered, but is not persuasive. Appellants' quote is taken from the reasoning of the court to allow an interference to proceed. The quoted idea of utility was what the Supreme Court set out to clarify and rectify with standing Court decisions. At 696, the Supreme Court stated that they "find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product." The Supreme Court also discussed (694):

> Even on the assumption that the process would be patentable were respondent to show that the steroid produced had a tumor-inhibiting effect in mice, [17]we would not overrule the Patent Office finding that respondent has not made such a showing. The Patent Office held that, despite the reference to the adjacent homologue, respondent's papers did not disclose a sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics. Indeed, respondent himself recognized that the presumption that adjacent homologues have the same utility [18]has been challenged in the steroid field because of "a greater known unpredictability of compounds in that field." [19] In these circumstances and in this technical area, we would not overturn the finding of the Primary Examiner, affirmed by the Board of Appeals and not challenged by the CCPA.

The above situation is analogous to that of the instant application because its claimed invention, the PRO1557 protein and related proteins have not been shown to have a sufficient likelihood of being used as a cancer diagnostic for the reasons previously discussed. Also, in the proteomic art there is a "known unpredictability" concerning the correlation of mRNA and protein levels.

Appellants discuss *In re Kirk (CCPA 1967)* on pages 42 and 48, in which the assertion that a man-made steroid with biological activity was insufficient without information in the specification as to how the biological activity could be practically used. This case does not refute the current rejections.

Appellants argue (pages 42-48) that in *Nelson v. Bowler*, the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. The argument has been fully considered, but is not persuasive. In *Nelson,* the court held that the compound of which utility was in question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility because the specification does not allow the skilled artisan to use the instant invention for the reasons previously discussed. It is maintained that the instant application has not established a correlation between higher expression of the PRO1557 mRNA and polypeptide or the diagnostic use of the encoded protein.

Appellants argue on pages 44-46 and 48-49 that the Court in *Cross v. Iizuka* reaffirmed that a "rigorous correlation" is not required to establish practical utility. The argument has been fully considered, but is not persuasive. The Court (at 739) said, "a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence". At issue in *Cross* was practical utility, and the Court held that there is (often) a reasonable correlation between *in vitro* and *in vivo* activity. Neither the PRO 1557 polynucleotide nor encoded polypeptide have been asserted to have a specific pharmacological activity. Instead they are said to have a specific diagnostic use. The arguments of pharmacological activity discussed in *Cross* and *Fujikawa* are, then, not directly related to the issues at hand.

On pages 44-47, Appellants also cite *Cross v. Iizuka* (Fed. Cir. 1985) and *Fujikawa v. Wattanasin* (Fed. Cir. 1996), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo*. The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: whether differences in expression of PRO1557 nucleic acid were significant, under what conditions differences could be detected, repeatability of the differential expression of PRO1557 polynucleotide both in terms of frequency/prevalence and quantity/sensitivity, what levels (relative or absolute) were detected in tumors, and whether mRNA levels correlated with encoded protein levels, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention.

Turning to the rejection under 35 USC, 112, first paragraph enablement, Appellants argue (p. 50) that based in part on "the disclosure in Example 18 of the instant application that the nucleic acid encoding the PRO1557 polypeptide is at least two-fold differentially expressed in esophageal and kidney tumor relative to normal esophageal and kidney tissue, respectively." The argument has been fully considered, but is not persuasive. There is nothing in Example 18 to indicate that the PRO1557 nucleic acid is two-fold differentially expressed. That opinion comes from the first declaration of Dr. Grimaldi submitted 4/13/05. Further, even assuming it is

two-fold differentially expressed, it is maintained for the reasons for record and as discussed above, that one of skill in the art would not reasonably expect that to be true of the PRO1557 protein because of the unpredictability of mRNA/protein level correlation studies in the art.

Appellants submit (pages 51-55) that because the claimed polypeptides have substantial, specific and credible utility, it is not proper to reject the claimed polypeptides as lacking enablement on a "lack of utility" basis. The argument has been fully considered, but is not persuasive. First, it is maintained that the invention does not have utility. Second, MPEP § 2107.01 states that "It is important to recognize that 35 U.S.C. 112, first paragraph, addresses matters other than those related to the question of whether or not an invention lacks utility. These matters include ... whether the applicant has provided an enabling disclosure of the claimed subject matter..." Third, while part of the reasoning for lack of enablement may be applicable to lack of utility, there are additional reasons as discussed in the previous Office action mailed 7/06/05 beginning bottom of p. 3:

> Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is [an antibody to] a polypeptide encoded by a nucleic acid with no known specific association other than that asserted by Applicants of higher expression in kidney and esophageal tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in kidney and esophageal tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical property. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though none as a tumor marker were identical or highly similar to SEQ ID NO:81. Therefore, the connection of SEQ ID NO:81 to tumors was not known. The prior art is silent with respect to activity of PRO1557 or its relationship to a family of proteins with conserved structure and function. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. The breadth of the claims is not at issue. There is very little guidance or direction

> about using the claimed antibody except that nucleic acid of SEQ ID NO:81 which encodes the cognate polypeptide is more highly expressed in kidney and esophageal tumors. As discussed in previous Office actions, the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

The above paragraph discusses factors to be considered for evaluating enablement of an invention, including nature of the invention, state of the prior art, level of predictability in the art, existence of working examples, breadth of claims and amount of direction or guidance by the inventors. It remains the Examiner's position that evaluation of enablement of the instant invention using the above considerations results in the conclusion that it would require undue experimentation to use the invention as claimed.

Appellants argue (pages 53-54 and middle of p. 58) that *Brana* is applicable to the present case because the enablement rejection is based on lack of utility and that the two types of rejection are the same in the instant case. The argument has been fully considered, but is not persuasive. It is not agreed that the enablement rejection is based **totally** on lack of utility, but in the present case the enablement rejection necessary relies to a large extent on the grounds for holding a lack of utility. However, just as with the related PRO1557 polynucleotide case, there are aspects of enablement separable from that of utility, since the polynucleotide remains not enabled. The two rejections in the instant case are separable and do not stand or fall together. The applicability of *Brana* was discussed in previous Office actions and is discussed above.

Appellants argue (p. 55) that the specification enables the claimed invention for making and using it. The argument has been fully considered, but is not persuasive. Appellants are directed to the paragraph two above this. It is maintained for the reasons of record that the specification is not enabling for how to use the instant invention.

Appellants argue (p. 56) that the nature of the invention is a polypeptide which may be used as a diagnostic, so the nature of the invention weighs in favor of enablement. The argument has been fully considered, but is not persuasive. The nature of the invention has to do not only with the fact that the invention is a polypeptide, but what characteristics are attributed to it. The sequence of the polypeptide is known, but its function is not. It is not known, for example, if it plays a role in causing cancer or if it binds a particular binding partner. That is what was meant

by the Examiner's statement that the claimed invention is a polypeptide without a "recognized/characterized physiological/biochemical property". It is maintained that the use of the polypeptide for a diagnostic purpose is not enabled.

Appellants argue (pages 55-57 and bottom of p. 62) that because methods of making and using polypeptides and making and using antibodies were known in the prior art, this factor weighs in favour of enablement. The argument has been fully considered, but is not persuasive. A generic use of a polypeptide, such as a weight marker on a gel, that is applicable to almost any polypeptide does not provide enablement for the claimed polypeptide. Likewise, making an antibody that recognizes a polypeptide which is not enabled does not support enablement for the antibody.

Appellants argue (pages 57-58) that differential nucleic acid screening is not relevant to determination of enablement, and as argued above in reference to expected correlation of mRNA level to protein level and applicability of *In re Brana,* one skilled in the art could use the claimed invention. The argument has been fully considered, but is not persuasive. The point the Examiner was trying to make about differential screening is that interpretation of results is based on many factors as illustrated by the work of Haynes et al., Hu et al. and Fessler et al. Also, Appellants are directed to the Examiner's discussion of mRNA/protein level correlation and *Brana* above.

Appellants argue (pages 58-59) that due to the level of skill in the art, the skilled artisan would have been able to predictably use the claimed antibody in diagnostic methods. The argument has been fully considered, but is not persuasive. It is maintained for the reasons of record that there is unpredictability relating to correlation or lack there of between levels of an mRNA and its encoded protein based on the proteomic art of record. As stated in the above *Wands* analysis of the final Office action of 07/06/05, "Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given."

Appellants argue (pages 59-61) that the specification provides sufficient guidance and direction in the specification for the skilled artisan to be able to use the claimed invention. The argument has been fully considered, but is not persuasive. For the reasons previously discussed, including the lack of predictability and limited teachings in the specification including relative or

absolute nucleic acid expression levels and repeatability of the differential expression of PRO1557 polynucleotide both in terms of frequency/prevalence and quantity/sensitivity, it is maintained that the skilled artisan could not use the claimed invention without undue experimentation.

Appellants argue (bottom of p. 61 through p. 62) that the presence of working examples weighs in favor of enablement. The argument has been fully considered, but is not persuasive. The working examples fail to support enablement and do not address the specific type of tumor tissue used, levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example.

Appellants argue (p. 63) that the fact that further experimentation is necessary or complex does not make the experimentation undue. The argument has been fully considered, but is not persuasive. Whether experimentation is undue is only one factor in determining enablement. For the polypeptide or binding antibody to be enabled, one skilled in the art must be able to use it based on the description in the specification, prior art and information generally available to one of skill in the art at the time the application was filed. Applicants are directed to the *Wands* analysis discussed above which provides reasoning why it would require undue experimentation to use the claimed invention.

Appellants argue (pages 63-65) that the *Wands* factors support enablement of the claimed invention and the Examiner has provided no significant evidence or argument to the contrary. The argument has been fully considered, but is not persuasive. It is maintained for the reasons previously set forth and as discussed above, the instant invention is not enabled. Appellants are referred to the discussions above that reference evidence and arguments that support the lack of enablement.

In addressing the rejection of claims under 35 USC 102, Appellants argue (pages 65-66) that the invention is entitled to a priority date no later than August 24, 2000. The argument has been fully considered, but is not persuasive. Because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, as discussed above, and the earlier application, likewise do not meet those requirements, the instant application does not receive benefit of priority to earlier

filed applications. Even though SEQ ID NO:81 and 82 and the expression information of Table 18 were previously disclosed, enablement thereof has not been established as discussed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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